

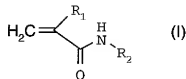
AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

LISTING OF CLAIMS:

1. (Previously Presented) A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient,

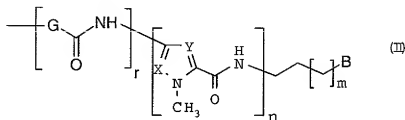
- an acryloyl distamycin derivative of formula (I):



wherein:

R₁ is a bromine or chlorine atom;

R₂ is a group of formula (II)



wherein

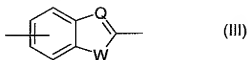
m is an integer from 0 to 2;

n is an integer from 2 to 5;

r is 0 or 1;

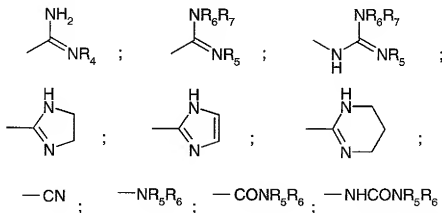
X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a group NR₃ wherein R₃ is hydrogen or C₁-C₄ alkyl;

B is selected from the group consisting of



wherein R₄ is cyano, amino, hydroxy or C₁-C₄ alkoxy; R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl; or a pharmaceutically acceptable salt thereof; and

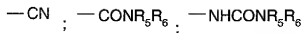
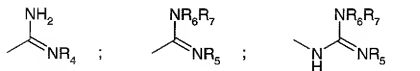
a protein kinase inhibitor; wherein said pharmaceutical composition has a synergistic antineoplastic effect.

2. (Original) A pharmaceutical composition according to claim 1 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, PKI 166, EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosine, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11248, Flavopiridol, and CI-202.

3. (Original) A pharmaceutical composition according to claim 2 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774 and SU 5416.

4. (Cancelled)

5. (Previously Presented) A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative of formula (I) wherein R₁ and R₂ are as defined in claim 1, r is 0, m is 0 or 1, n is 4, X and Y are both CH groups and B is selected from:



wherein R₄ is cyano or hydroxy and R₅, R₆ and R₇, the same or different, are hydrogen or C₁-C₄ alkyl.

6. (Original) A pharmaceutical composition according to claim 5 comprising an acryloyl distamycin derivative of formula (I) wherein R₁ is bromine, R₂ is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH, B is a group of formula



wherein R₅, R₆ and R₇ are hydrogen atoms, optionally in the form of a pharmaceutically acceptable salt.

7. (Currently Amended) A pharmaceutical composition according to claim 1 comprising an acryloyl distamycin derivative, optionally in the form of a pharmaceutically acceptable salt, selected from the group consisting of:

[[1.]] N-(5-{{[(5-{{[(5-{{[(2-{{[amino(imino)methyl]amino}ethyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

[[2.]] N-(5-{{[(5-{{[(5-{{[(2-{{[amino(imino)methyl]amino}propyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

[[3.]] N-(5-{{[(5-{{[(5-{{[(3-amino-3-iminopropyl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)amino]carbonyl}-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

[[4.]] N-(5-{{(5-{{(3-amino-3-iminopropyl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-imidazole-2-carboxamide hydrochloride;

[[5.]] N-(5-{{(5-{{(3-amino-3-iminopropyl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide hydrochloride;

[[6.]] N-(5-{{(5-{{(3-amino-3-oxopropyl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)-3-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrazole-5-carboxamide;

[[7.]] N-(5-{{(5-{{(2-{{[amino(imino)methyl]amino}ethyl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-chloroacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

[[8.]] N-(5-{{(3-{{[amino(imino)methyl]amino}propyl)amino}carbonyl)-1-methyl-1H-pyrrol-3-yl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride;

[[9.]] N-(5-{{(3-amino-3-iminopropyl)amino}carbonyl)-1-methyl-1H-pyrrol-3-yl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride; and

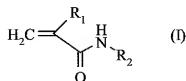
[[10.]] N-{5-[(5-[(3-[(aminocarbonyl)amino]propyl)amino]carbonyl)-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)amino]carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide.

8. (Original) A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and, as active ingredient,

- N-(5-{{(5-{{(2-{{[amino(imino)methyl]amino}ethyl)amino}carbonyl)-1-methyl-1H-pyrrol-3-yl)amino}carbonyl}-1-methyl-1H-pyrrol-3-yl)amino}carbonyl]-1-methyl-1H-pyrrol-3-yl)-4-[(2-bromoacryloyl)amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin); and

- a protein kinase inhibitor selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

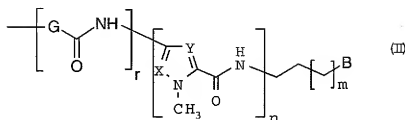
9. (Currently Amended) Product comprising an acryloyl distamycin derivative of formula (I):



wherein:

R₁ is a bromine or chlorine atom;

R₂ is a group of formula (II)



wherein

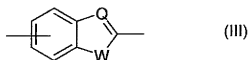
m is an integer from 0 to 2;

n is an integer from 2 to 5;

r is 0 or 1;

X and Y are, the same or different and independently for each heterocyclic ring, a nitrogen atom or a CH group;

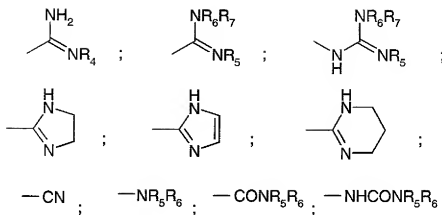
G is phenylene, a 5 or 6 membered saturated or unsaturated heterocyclic ring with from 1 to 3 heteroatoms selected among N, O or S, or it is a group of formula (III) below:



wherein Q is a nitrogen atom or a CH group and W is an oxygen or sulfur atom or it is a group NR₃;

wherein R₃ is hydrogen or C₁-C₄ alkyl;

B is selected from the group consisting of



wherein R_4 is cyano, amino, hydroxy or $\text{C}_1\text{-C}_4$ alkoxy; R_5 , R_6 and R_7 , the same or different, are hydrogen or $\text{C}_1\text{-C}_4$ alkyl;

or a pharmaceutically acceptable salt thereof; and

a protein kinase inhibitor, as a ~~combined~~ preparation where the acryloyl distamycin derivative may be administered simultaneously with the protein kinase inhibitor or, alternatively, both compounds may be administered sequentially in either order for simultaneous, separate or sequential use in the treatment of tumors.

10. (Previously Presented) Product according to claim 9 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, PKI 166, EKB-569, GW572016, CEP 2563, UCN-01, GCP 41251 (STI 412), Safingol, Perifosine, SU 5416, CGP 79787, CP-564959, ZD 6474, ZD 2171, SU-11248, Flavopiridol, and CI-202.

11. (Previously Presented) Product according to claim 10 wherein the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774 and SU 5416.

12. (Cancelled)

13. (Previously Presented) Product according to claim 9 comprising an acryloyl distamycin derivative of formula (I) wherein R_1 is bromine, R_2 is a group of formula (II) wherein r and m are 0, n is 4, X and Y are CH , B is a group of formula



wherein R₅, R₆ and R₇ are hydrogen, optionally in the form of a pharmaceutically acceptable salt.

14. (Previously Presented) Product according to claim 9 wherein the acryloyl distamycin derivative is selected from the group as defined in claim 7.

15. (Previously Presented) Product comprising the acryloyl distamycin derivative N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Bristollicin), and a protein kinase inhibitor selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416; as a combined preparation for simultaneous, separate or sequential use in the treatment of tumors.

16.-23. (Cancelled)

24. (Original) A method of treating a mammal, including humans, suffering from a neoplastic disease state, which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

25. (Original) A method according to claim 24 wherein the acryloyl distamycin derivative is N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl[carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Bristollicin), and the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

26. (Original) A method for lowering the side effects caused by antineoplastic therapy with an antineoplastic agent, in a mammal in need thereof including humans, the method comprising administering to said mammal a combined preparation comprising a protein kinase inhibitor and an acryloyl distamycin derivative of formula (I), as defined in claim 1, in amounts effective to produce a synergistic antineoplastic effect.

27. (Original) A method according to claim 26 wherein the acryloyl distamycin derivative is N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (Brostallicin), and the protein kinase inhibitor is selected from the group consisting of STI571, ZD-1839, OSI-774, and SU 5416.

28. (Previously Presented) A method according to claim 24 wherein said disease state is selected from breast, ovary, lung, colon, kidney, stomach, pancreas, liver, melanoma, leukemia and brain tumors.

29. (Previously Presented) A method of treating metastasis suffered by a mammal, including humans, which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.

30. (Previously Presented) A method of treating tumors in a mammal, including humans by inhibition of angiogenesis, which method comprises administering to said mammal the acryloyl distamycin derivative of formula (I), as defined in claim 1, and a protein kinase inhibitor, in amounts effective to produce a synergistic antineoplastic effect.